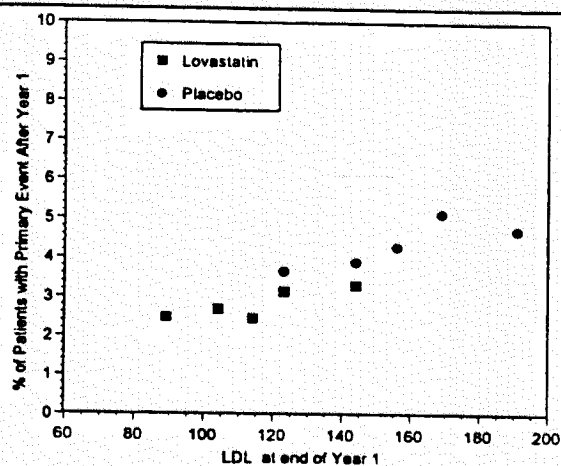Figure 4 Relationship between LDL at the end of Year 1 and subsequent primary events observed by treatment group. Points correspond to the mean of the treatment group LDL quintile on the x-axis

To study the relationship between LDL level and event rates, FDA performed an analysis similar to an analysis of 4S data reported by Pedersen et al (Circulation 1998;97:1453-1460). The results are depicted in Figure 4 (this figure is similar to Figure 4 in the aforementioned paper). These results suggest that the incidence of primary events is slightly graded over the observed range of LDL and that benefit due to lovastatin over placebo is evident (but not statistically significant) when LDL levels are comparable (see points for LDL of about 125 to 145).

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Results for subgroups defined by age, gender and baseline LDL

Analyses were performed for subgroups defined by gender, age and baseline LDL (Table 12). Most of the events were observed in males, in patients under 65 years olds and in patients with LDL of 130 or greater; treatment differences, also, are most impressive in those subgroups.

The number of events for women was very low so that small shifts in the events could result in big changes to the estimates; therefore the results for women are only suggestive of a benefit. Also, similarly, the effect of lovastatin on the primary efficacy endpoint could not be adequately assessed in diabetics because there were too few events (a total of 10 events).

Table 12.   AFCAPS
Primary Endpoint Results by Subgroups based on Age, Gender and Baseline LDL

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
Gender					
Male	109/2805 (3.9%)	170/2803 (6.1%)	0.63	0.50, 0.81	.0002
Female	7/499 (1.4%)	13/498 (2.6%)	0.54	0.22, 1.36	.19
Gender by Median Age					
Male					
Age≤57	33/1444 (2.3%)	64/1455 (4.4%)	0.51	0.34, 0.78	.002
Age>57	76/1361 (5.6%)	106/1348 (7.9%)	0.71	0.53, 0.95	.02
Female					
Age≤62	5/268 (1.9%)	7/258 (2.7%)	0.71	0.22, 2.23	.55
Age>62	2/231 (0.9%)	6/240 (2.5%)	0.34	0.07, 1.67	.18
Age					
<65	73/2589 (2.8%)	126/2600 (4.9%)	0.58	0.43, 0.77	.0002
≥65	36/612 (5.9%)	53/594 (8.9%)	0.66	0.43, 1.00	.052
Median Baseline LDL					
<149.3	55/1663 (3.3%)	78/1641 (4.8%)	0.69	0.49, 0.98	.04
≥149.3	61/1641 (3.7%)	105/1660 (6.3%)	0.58	0.42, 0.79	.0007
Baseline LDL					
<130	14/348 (4.0%)	21/343 (6.1%)	0.65	0.33, 1.28	.21
≥130	102/2956 (3.5%)	162/2458 (5.5%)	0.62	0.49, 0.80	.0002
Baseline LDL					
<160	76/2402 (3.2%)	119/2381 (5.0%)	0.63	0.47, 0.84	.002
≥160	40/902 (4.4%)	64/920 (7.0%)	0.63	0.42, 0.93	.02

Subgroups defined by risk factors:

Analyses were performed for subgroups defined by baseline risk factors (smoking, HDL hypertension and family history of CHD) and by number of risk factors alone and in relation to LDL.

Table 13. AFCAPS
Primary Endpoint Results by Subgroups based on CHD Risk Factors

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
Smoker					
Yes	17/429 (4.0%)	36/389 (9.3%)	0.41	0.23, 0.73	.002
No	99/2875 (3.4%)	147/2912 (5.1%)	0.68	0.52, 0.87	.003
Baseline HDL-C (mg/dl)					
<35	42/1150 (3.7%)	74/1146 (6.5%)	0.56	0.38, 0.81	.002
≥35	74/2154 (3.4%)	109/2155 (5.1%)	0.68	0.50, 0.91	.009
Hypertension					
Yes	38/719 (5.3%)	62/729 (8.5%)	0.62	0.41, 0.92	.019
No	78/2585 (3.0%)	121/2572 (4.7%)	0.63	0.48, 0.84	.002
Family HX of CHD					
Yes	25/497 (5.0%)	37/538 (6.9%)	0.72	0.43, 1.20	.21
No	91/2807 (3.2%)	146/2763 (5.3%)	0.61	0.47, 0.79	.0002
Risk factors					
1	31/1241 (2.5%)	37/1229 (3.0%)	0.83	0.51, 1.34	.44
≥2	85/2063 (4.1%)	146/2072 (7.1%)	0.58	0.44, 0.75	.0001
Risk factors					
1	31/1241 (2.5%)	37/1229 (3.0%)	0.83	0.51, 1.34	.44
2	52/1371 (3.8%)	87/1398 (6.2%)	0.60	0.43, 0.85	.004
≥3	33/692 (4.8%)	59/674 (8.8%)	0.54	0.35, 0.82	.004
Baseline LDL≥160					
+ ≥2 risk factors *	27/530 (5.1%)	53/566 (9.4%)	0.53	0.34, 0.85	.008
Other	89/2774 (3.2%)	130/2735 (4.8%)	0.67	0.51, 0.88	.004
Baseline LDL <160					
<2 risk factors	18/869 (2.1%)	26/875 (3.0%)	0.70	0.38, 1.27	.24
≥2 risk factors	58/1533 (3.8%)	93/1506 (6.2%)	0.60	0.44, 0.84	.003
Baseline LDL ≥160					
<2 risk factors	13/372 (3.5%)	11/354 (3.1%)	1.13	0.50, 2.51	.77
≥2 risk factors *	27/530 (5.1%)	53/566 (9.4%)	0.53	0.34, 0.85	.008
Baseline LDL≥130					
+ ≥2 risk factors	71/1823 (3.9%)	130/1849 (7.0%)	0.55	0.41, 0.73	.0001
Other	45/1436 (3.0%)	53/1452 (3.7%)	0.83	0.56, 1.24	.36
Baseline LDL <130					
<2 risk factors	0/108 (0%)	5/120 (4.2%)	—	—	.99
≥2 risk factors	14/240 (5.8%)	16/223 (7.2%)	0.79	0.38, 1.62	.52
Baseline LDL ≥130					
<2 risk factors	31/1133 (2.7%)	32/1109 (2.9%)	0.94	0.57, 1.54	.81
≥2 risk factors	71/1823 (3.9%)	130/1849 (7.0%)	0.55	0.41, 0.73	.0001

* Subgroup of patients that would be recommended for lipid-lowering treatment based on the NCEP guidelines of LDL≥160 and ≥2 risk factors

Consistent risk reductions with lovastatin use were demonstrated in hypertensives/non-hypertensives and smokers/non-smokers and for subgroups based on HDL above and

below 35. The sponsor also looked at the ratio of TC to HDL using a cutpoint of 5 and found significant risk reductions in both subgroups. Using a cutpoint of 6, the median ratio in the cohort, the relative risk for patients with ratios of 6 or greater was 0.58 (p=.0005) and for patients with a ratio less than 6, 0.69 (p=.042).

Participants with $\geq$ 2 risk factors and randomized to lovastatin had significant risk reductions compared to the placebo group and this effect was evident across a range of LDL-C levels > 130 mg/dL. Interestingly, the placebo event rate for those participants with $\geq$ 2 risk factors (6.2-9.4%) was higher than the placebo event rate for the entire cohort (5.5%) and a significant number of primary endpoint events occurred in this subgroup (231/299 events or 77%).

Conclusions from the Primary Endpoint Results

Treatment of the AFCAPS/TexCAPS cohort with lovastatin 20 to 40 mg daily resulted in a significant reduction in the rate of combined primary events comprised of sudden death, fatal and nonfatal MI, and unstable angina. The majority of the events were nonfatal MIs and unstable angina. Seventy-seven percent of all primary endpoints were experienced by those participants with $\geq$ 2 risk factors for CHD and this subgroup derived a significant risk reduction when treated with lovastatin.

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